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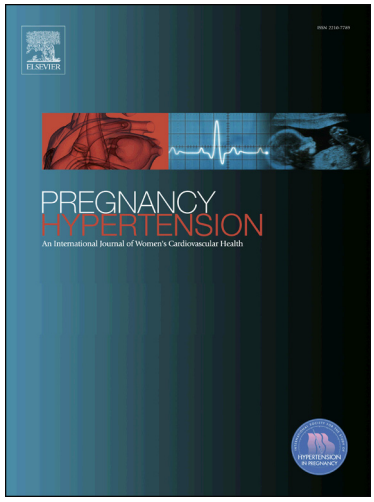


Fetal size and growth velocity in chronic hypertension

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**TITLE PAGE**

**Title: Fetal size and growth velocity in chronic hypertension.**

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**Conflict of interests**

The Authors disclose no conflict of interest nor relevant financial interest.

**Ethics disclosure**

The Cambridge research ethics committee advised that analysis and publication of routinely collected, fully anonymised obstetric growth measurements used as part of normal clinical management did not require approval.

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**ABSTRACT**

**Objective:** To investigate longitudinal fetal growth and growth velocity for commonly measured biometric parameters in women with chronic hypertension.

**Methods:** Two centre retrospective European study of women with chronic hypertension ascertained at pregnancy booking. Ultrasound measurements of head circumference (HC), abdominal circumference (AC) and femur length (FL) were used to derive longitudinal fetal growth charts derived using functional linear discriminant analysis (FLDA). These were compared to existing cross sectional and longitudinal charts, as was birthweight.

**Results:** 282 women with a median of 3 third trimester ultrasound examinations were included. Gestation at delivery was 37.5 weeks (SD 2.68), birthweight 3049 g (SD 785). Birthweight <10$^{th}$ percentile found in 15.6% deliveries, >90$^{th}$ percentile 20.2%. Fetal size curves derived from women with chronic hypertension were no different to cross sectional and longitudinal charts for a normal population. Compared to a standard longitudinal biometry chart, growth velocity (mm/day) in chronic hypertension was higher for AC and FL at 30-32 weeks (AC 1.447 vs 1.357 $p<0.05$; FL 0.296 vs 0.269 $p<0.01$) and 34-36 weeks (AC 1.325 vs 1.140 $p<0.01$; FL 0.248 vs 0.198 $p<0.01$).

**Conclusions:** In women with chronic hypertension there is an excess of both SGA and LGA babies compared to population standards. Growth velocity of the AC and FL was greater after 30 weeks compared to a normal population.

**KEY WORDS:** abdominal circumference, biparietal diameter, femur length, FLDA, head circumference

## LIST OF ABBREVIATIONS

- BMI: body mass index
- GDM: gestational diabetes mellitus
- SGA: small for gestational age
- LGA: large for gestational age
- HC: head circumference
- AC: abdominal circumference
- FL: femur length
- BPD: biparietal diameter
- FLDA: functional linear discriminant analysis
- US: United States
- UK: United Kingdom

## KEY MESSAGE

In chronic hypertensive pregnant women fetal growth patterns differ from those of uncomplicated pregnancies.

# FETAL SIZE AND GROWTH VELOCITY IN CHRONIC HYPERTENSION

## INTRODUCTION

Chronic hypertension affects up to 5% of pregnancies, but recent demographic analysis suggests that its incidence is increasing. Reasons for this include maternal age, the increasing tendency of women with chronic disease becoming pregnant, obesity and women with one or more of these attributes having access to assisted reproduction techniques.

Chronic hypertension is associated with an increased risk of maternal and fetal complications. A recent meta-analysis of 795221 cases of chronic hypertensive pregnancies reported the incidence of superimposed preeclampsia to be 29%, Cesarean delivery 42% and perinatal death rate of 3-5%. Adverse perinatal outcomes are secondary to placental abruption, preterm birth (33%) and birth weight below 2500 g (22%) (1,2). Poor pregnancy outcome is not related to a particular threshold of blood pressure nor to the degree of blood pressure control. Apart from some beta blockers, antihypertensive drugs are not associated with a higher incidence of growth restriction or poor perinatal outcome (3,4).

Women with chronic hypertension invariably attend more frequently for ultrasound scans of the fetus, principally to check growth. In the United Kingdom, National Institute of Clinical Excellence (NICE) guidance suggests third trimester ultrasound scans in view of the risk of fetal growth restriction in pregnancies (5) and this advice is ubiquitous in other national guidelines included that of the American College of Obstetricians and Gynecologists (6). There is growing debate about appropriate reference values for fetal growth in healthy women, with controversy between those reporting similar fetal growth irrespective of geographical location (7) and those finding small differences between populations (8). Similarly, there is no reliable data relating to fetal growth in women with chronic hypertension; all assumptions are back-calculated from birthweight. We do not advocate the

use of fetal size charts customized for maternal pathological condition, but such data may be useful in understanding how growth differs compared to normal.

The aim of this study of pregnant women with chronic hypertension was to determine whether fetal growth velocity deviates from normal in the third trimester by comparing fetal size at different gestation points (longitudinal growth) to widely used reference charts. From this, we planned to derive growth velocity as the derivative of change in size with respect to time (*dx/dt*), comparing this to an established longitudinal fetal growth velocity chart to determine if and at which gestation point growth velocity deviates from normal.

## METHODS

This was a database search of all pregnant women with a singleton pregnancy and known diagnosis of chronic hypertension before pregnancy or of hypertension before 20 weeks of gestation. Data were collected from the Rosie Maternity Department at Addenbrooke's Hospital in Cambridge, UK, between January 2002 and December 2011 which over the study period had approximately 5000 births annually and from Fetal-Maternal Unit in Spedali Civili of Brescia, Italy, between January 2008 and December 2012 which had approximately 4000 births yearly.

All pregnancies underwent first trimester ultrasound and an ultrasound scan at 19-21 weeks of gestation and the frequency of third trimester ultrasound scans was according to local protocols. Age, parity, ethnicity, BMI, smoking, alcohol consumption, significant comorbidity, pharmacological therapy, delivery data including gestational age at delivery and outcome of pregnancy, birthweight, sex of the fetus, delivery type, Cesarean section indications, Apgar score, NICU admission were collected. Women with additional comorbidities such as Systemic Lupus Erythematosus or chronic kidney disease were not included. For each scan, we collected fetal biometric parameters including the head circumference (HC), the abdominal circumference (AC) and the femur length (FL), while

In Cambridge, ultrasound biometry data were collected using the Rosie Maternity Hospital's software, Protos® and Astraia© for ultrasound data; in Brescia from the Materno-Fetal software, Viewpoint®. For the few patients who did not deliver at the Spedali Civili di Brescia data related to the outcome of pregnancies were collected from the hospitals where the patients delivered. Data were entered on a separate database with restricted access on the hospital servers and fully anonymised prior to analysis.

The Cambridge research ethics committee advised that analysis and publication of routinely collected, fully anonymised obstetric growth measurements entered into an ultrasound software system as part of normal clinical management did not require approval.

Maternal age, BMI and parity for the chronic hypertension group were compared between the chronic hypertensive women and a control population (9), using either a Pearson's chi-square test (BMI group and parity) or a Fisher's exact test (maternal age group).

At least 2 scans per case were required for growth curve creation; women with AC, HC and FL measurements at only 1 time point were dropped, leaving 223 cases. Longitudinal growth curves were then created using Functional Linear Discriminant Analysis software (10). After the calculation of the growth curve, we restricted comparisons between the chronic hypertension group and the normal population (9) to be between 20 and 36 weeks due to the sparsity of the data outside of this time period. Empirical p-values were then calculated at 9 time points, starting at 20 weeks and increasing at 2 week intervals, to test for differences in growth between the chronic hypertensive group and the control population.

Growth curves for fetal biometry were created using regression methods outlined in Verburg, 2008 (11). Each scan is assumed to be an independent observation, and so the sample sizes for AC, HC and FL respectively were 824, 816 and 823. We used these curves to calculate the growth velocities for each measurement type (AC, HC, FL) between 26-28 weeks, 30-32 weeks and 34-36 weeks. The growth curves for a normal population from Verburg et. al., 2008 (11) were used as the controls. Empirical p-values were calculated for each time interval, and for each measurement type, to test if the growth velocities of the chronic hypertension cases differed to those of the control population.

For a given measurement type and time interval a sample of normal growth velocities was generated (sample sizes for AC, HC and FL analysis were as above). The mean growth

velocity was recorded and this was repeated 10,000 times. The resulting distribution of expected growth velocities for the normal population was then used to calculate the empirical p-value. This is the number of values more extreme than the chronic hypertension group mean divided by the number of values available (10,000 in this case).

Using equations derived by Hadlock et. al., 1991 (12), we calculated the birthweight percentile for each hypertensive case using 'normal' pregnancy inputs. This allowed us to compare gestational-age adjusted birthweights of the chronic hypertensive and normal populations by looking at hypertension birthweights as a percentile of the normal population birthweight distribution. Inputs used were mean birth weight at 40 weeks for a normal population and standard deviation (3400 g and 449.79 g, respectively) (9). If there was no difference between the birth weights of the hypertensive population and the control population then we would expect to see an approximately uniform distribution for the calculated birthweight percentiles. The proportion of small for gestational age (SGA) and large for gestational age (LGA) babies from chronic hypertensive mothers were then compared to the expected proportions from the control population (11) using empirical p-values.

For a normal population we would expect the birthweight percentile distribution to be uniform. 282 normal pregnancy birthweight percentiles were generated, and the proportion of SGA cases (birthweight percentile < 10th percentile) and LGA cases (birthweight percentile > 90th percentile) were recorded. This was repeated 10,000 times so that we generated distributions for the proportion of SGA babies and LGA babies from normal pregnancies when the sample size = 282. The empirical p-value is then the proportion of values more extreme than that observed in the chronic hypertension group.

## RESULTS

Two hundred and eighty two chronic hypertensive women were analyzed whose demographic data are shown in Table 1. Of 282 women 134 (48%) were on antihypertensive therapy: 79 were taking calcium antagonists, 29 beta blockers, 7 alpha-methyldopa, 16 combination therapy and 3 other treatments.

282 women were with 1-6 scans were included. For the purposes of growth and growth velocity assessment, we analyzed the data from 223 women who had at least 2 scans (Table 2). Figure 1 shows the birth weight percentile distribution within the study group and the expected birth weight percentile distribution in the reference population. Figures 2a, 3a and 4a show the scatter plots for AC, HC and FL in 223 women. Figures 2b, 3b and 4b demonstrate the FLDA derived growth percentiles compared to the cross-sectional reference fetal growth charts. No differences were found for fetal AC, HC and FL 50$^{th}$ percentile between the FLDA and reference chart at any gestational time points.

HC and AC are normally distributed at the 3 time points where most measurement data are available according to a Shapiro-Wilks and an Andersen-Darling test for normality. There is evidence that FL is non-normal at 20 and 24 weeks according to these 2 tests but the distribution histograms allow the data to be analysed assuming normality (Supplementary Figure 5).

Table 3 shows the growth velocity for AC, HC and FL for the normal population based on reference charts and those with chronic hypertension. There were no differences between the three growth parameters at 26-28 weeks. For both later time points 30-32 and 34-36 weeks, AC and FL growth velocity was greater in the chronic hypertension group compared to growth velocities in a normal population.

Delivery outcomes are detailed in table 1. The mean gestation at delivery was 37.5 weeks (SD 2.78) and birth weight 3049 g (SD 785) was similar in the two centers. Forty-eight percent of all deliveries were by cesarean section. The incidence of superimposed preeclampsia was 12.8%, gestational diabetes 12% and of stillbirth was 0.7%.

Demographic and delivery data were compared with a recently reported and independent UK reference pregnant population (9). The age distribution for hypertensive women is older, with 50.5% being > 35 years compared to >16% for the reference population (Fisher's exact test $p<0.01$) ; parity greater with fewer para 0 and more para ≥1 women (Pearsons Chi square $p<0.01$) and higher BMI with 16% BMI ≥35 compared to 7.5% (Pearsons Chi square test $p<0.01$).

Within the same group birthweight <10$^{th}$ percentile and >90$^{th}$ percentile were found in 15.6% and 20.2% of the deliveries respectively, this being different to the proportion expected based on the comparator population (p 0.045 and p <0.01, respectively). When women with GDM were excluded, the proportion of birthweight <10$^{th}$ percentile was 14.3% and birthweight >90$^{th}$ percentile was 17.2%, again different to the comparator population ($p=0.016$ and $p<0.01$ respectively). When compared to a Scottish birth cohort (13), there was a significant excess of obese and morbidly obese women in all three birthweight groups SGA, normal and LGA (Fisher's exact $p<0.0001$).

## DISCUSSION

Fetal size and growth velocity have been little studied in maternal or fetal disease. Hence our aim in this study was not to construct 'normal' curves for women with chronic hypertension, but to investigate birth weight and growth velocity in this condition and to compare with what is already known in a normal population. This approach is methodologically different to customization as we describe fetal growth and birthweight in maternal pathology, observing the influences on growth and birthweight but not attempting to adjust for these. A similar approach has been recently reported for fetal growth in gastroschisis (1).

We report that mean birthweight is no different in women with chronic hypertension, although babies weighing $<10^{th}$ and those weighing $>90^{th}$ percentile are significantly over-represented, the latter particularly so. Of note is that just under half the women were on anti-hypertensive agents but their birthweight was no different to those of the cohort overall. Furthermore, based on data from repeat ultrasound examinations in over 200 women, fetal cross-sectional biometry in the third trimester of pregnancy is no different in chronic hypertension compared to cross sectional ultrasound standards. However, growth velocity (defined as change in size with time, rather than absolute size) for the fetal abdomen and femur is greater in women with chronic hypertension after 30 weeks compared to that expected in a normal population. Hence though overall in-utero fetal size is no different in chronic hypertension compared to widely used normal ranges, the percentile ranges that we observe in chronic hypertension are wider than those of the standard charts in the third trimester

A strength of the study is that all cases of chronic hypertension were ascertained prior to 20 weeks and followed throughout pregnancy in both units. We therefore did not include patients in whom a retrospective diagnosis of chronic hypertension was given. Perhaps for these

reasons, the proportion of chronic hypertensive pregnancies that we report in our population of approximately 0.4% is lower than the 1.3% reported for a US population ascertained at delivery (15). There is no reason why this should have biased the data though it is possible that the better than expected pregnancy outcomes with a superimposed preeclampsia risk of 12.8% and stillbirth risk 0.7% were because the women were closely monitored from the first trimester onwards (4,16).

The maternal characteristics of our population of women with chronic hypertension were different to a normal population: they had higher maternal age, parity and BMI compared to an unselected booking population from the West Midlands of the UK in the same period (9,17). Though none of the women had pre-existing insulin dependent diabetes, 12% (33/280) developed gestational diabetes which is more frequent than the general population incidence of 7% reported for a US population (15). Excluding women with GDM did not alter the findings of an excess in both $<10^{th}$ percentile and $>90^{th}$ percentile babies.

Women with hypertension and diabetes are more likely to have a raised BMI and be older; this is the case in the cohort that we recruited but we did not customize birth weight for maternal factors. Whilst the significantly increased BMI in this population of hypertensive women (across all birthweight percentiles) might explain at least partly the increased incidence of birthweight $>90^{th}$ percentile, the same explanation cannot be put forward to explain the increase in babies weighing $<10^{th}$ percentile.

The question of whether birth weight customization is appropriate is now particularly topical in the context of the findings from the Intergrowth study (7). This study had strict criteria resulting in only around 35% of all women being eligible for their ultrasound data to be used for construction of the charts. All of our cases, being hypertensive, would have been excluded from the Intergrowth study. Our data have instead been transposed onto the most widely

available cross sectional growth charts (11) and growth velocity has been derived from the only population based longitudinal growth charts from which growth velocity as opposed to fetal size at a given gestation can be calculated (18). The methodology that we have employed to develop fetal HC, AC and FL biometry charts is different to that used in the original development of the standard charts widely used for cross sectional ultrasound biometry (10). Using this methodology (functional linear discriminant analysis: FLDA), the use of all fetal size datapoints in a combined spline curve does not allow the cases with the most observations, and perhaps the most severe disease phenotype, undue influence over the final model. The FLDA technique has been reported for first trimester longitudinal size (19) and fetal growth in gastroschisis and growth restriction (14). The advantage of FLDA is that it is robust for a dataset of women where cases have repeated measures which are irregularly spaced and varying in number as all are converted to individual curves. To derive fetal growth velocity curves for the purposes of our comparisons, at least two observations per women were required.

An excess of small for gestational age babies has been reported in women with chronic hypertension (1, 16) which has been taken to imply that fetal growth must also be impaired. From this assumption has arisen recommendations for increased ultrasound surveillance of these pregnancies (3, 20). To our knowledge, no studies have considered actual fetal growth in chronic hypertension as opposed to inferring it from cohort studies of birthweight.

We found that both SGA and LGA babies are over-represented compared to a normal birth weight distribution. This has not been previously appreciated and is unlikely to be a chance observation as we also report an increase in growth velocity for the fetal abdomen and femur after 30 weeks. These findings might be explained at least in part by the higher incidence of gestational diabetes and the greater BMI in this population consistent with the hypothesis that an underlying metabolic disorder is more common in chronic hypertensive patients.

It is possible that chronic hypertension in pregnancy is associated with pre-existing maternal characteristics that affect fetal growth and potentially neonatal wellbeing. A recent meta-analysis showed that the relative risk for delivery of a <2.5kg baby was 2.7 for women with chronic hypertension though the relative risk for perinatal death was 4.2 (1) however this study did not consider the equivalent relative risks for delivery of a large baby. Our results raise the question as to whether the increased perinatal risks associated with chronic hypertension are indeed purely due to fetal growth impairment.

**ACKNOWLEDGEMENTS**

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**Figure 1: Histogram showing the distribution of the birthweight centile within the hypertension (HT) group and the expected distribution within the control group (in Blue).**

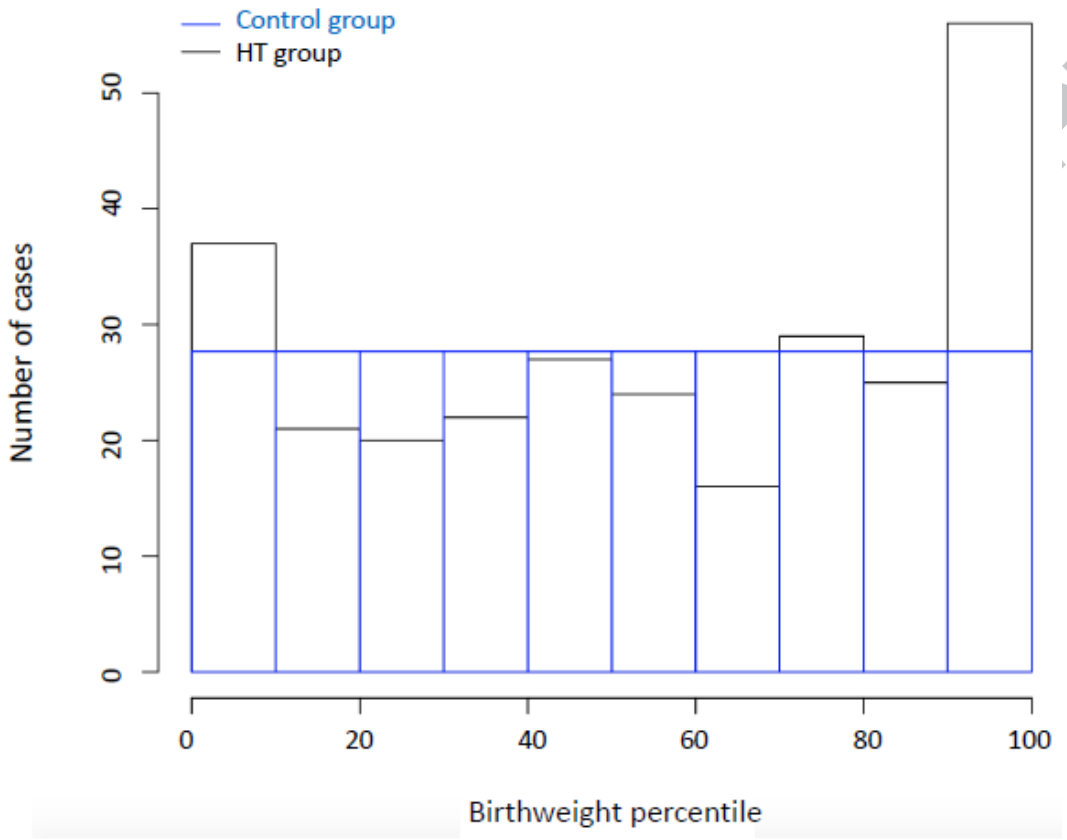
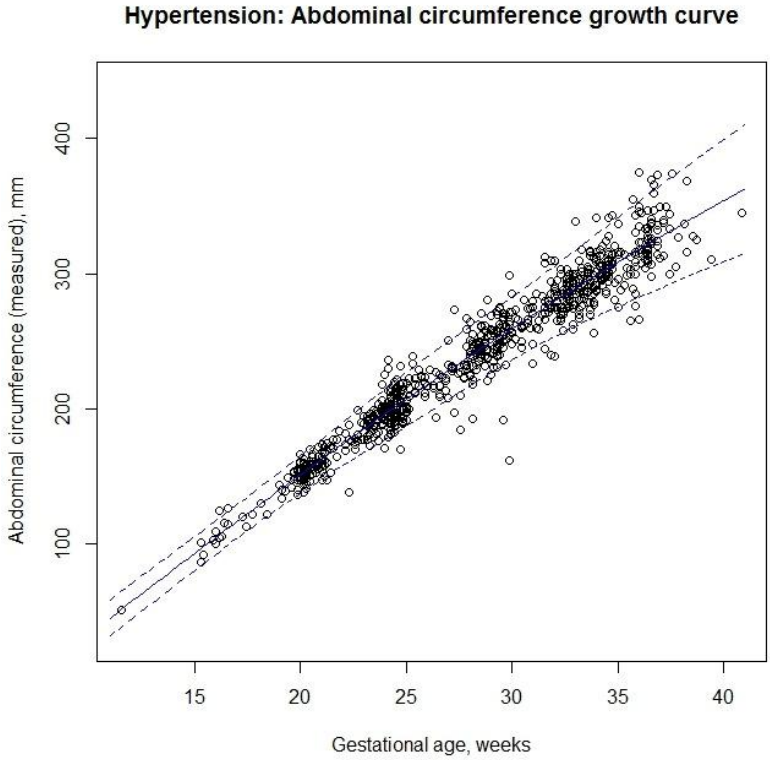


**Figure 2 (a) Abdominal circumference scatter diagram (b) transformation by FLDA onto cross sectional charts (Chitty)**



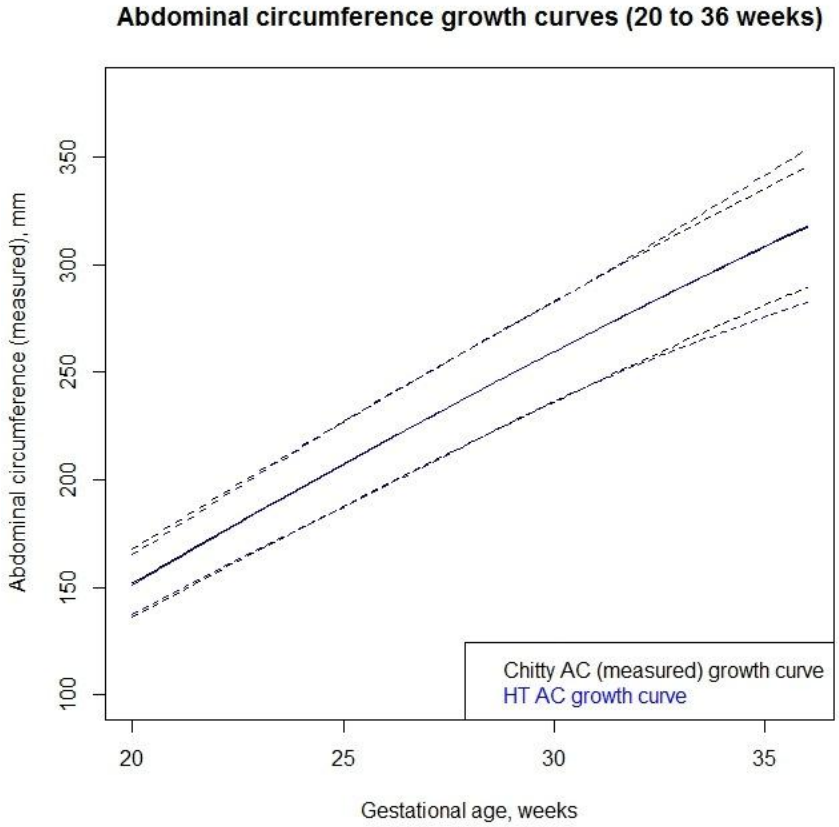
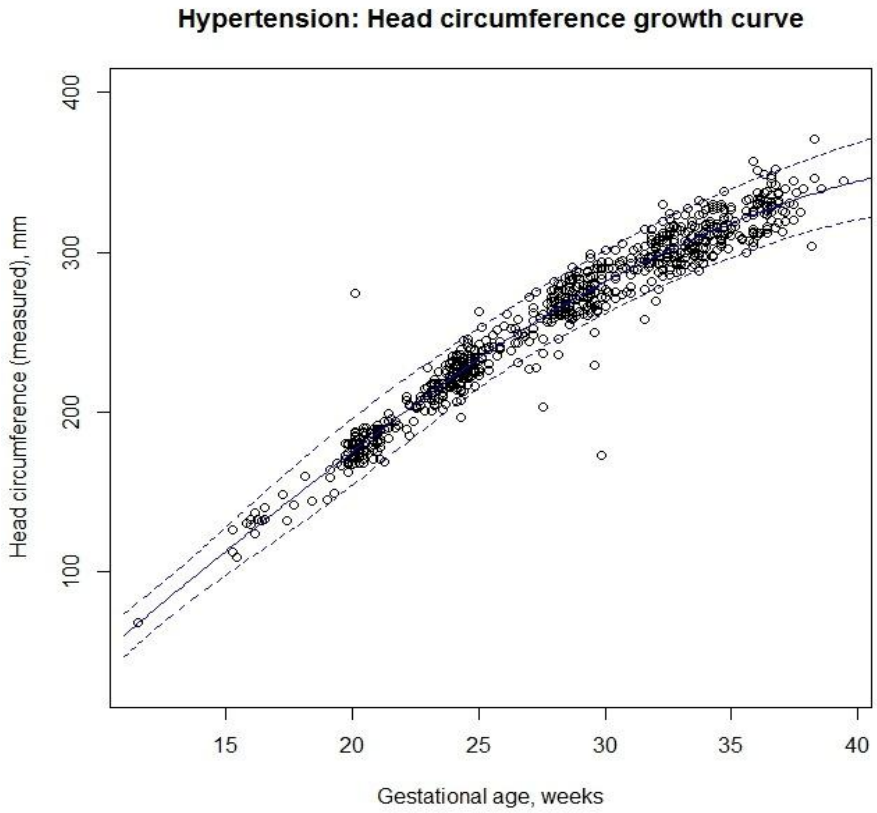



**Figure 3 (a) Head circumference scatter diagram (b) transformation by FLDA onto cross sectional charts (Chitty)**



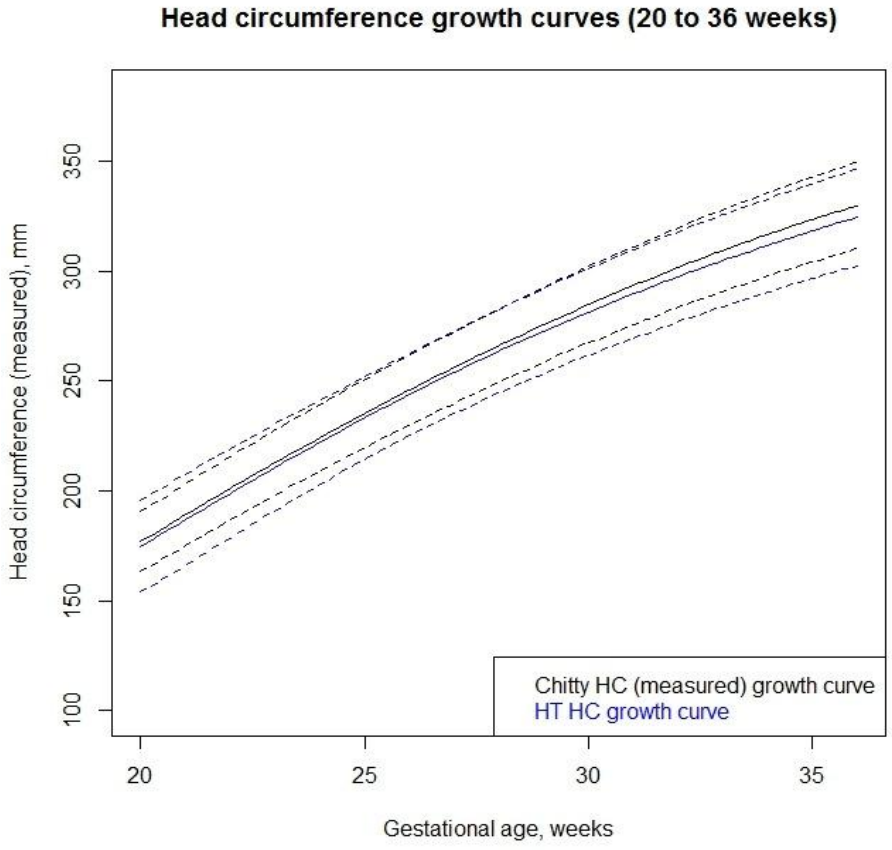
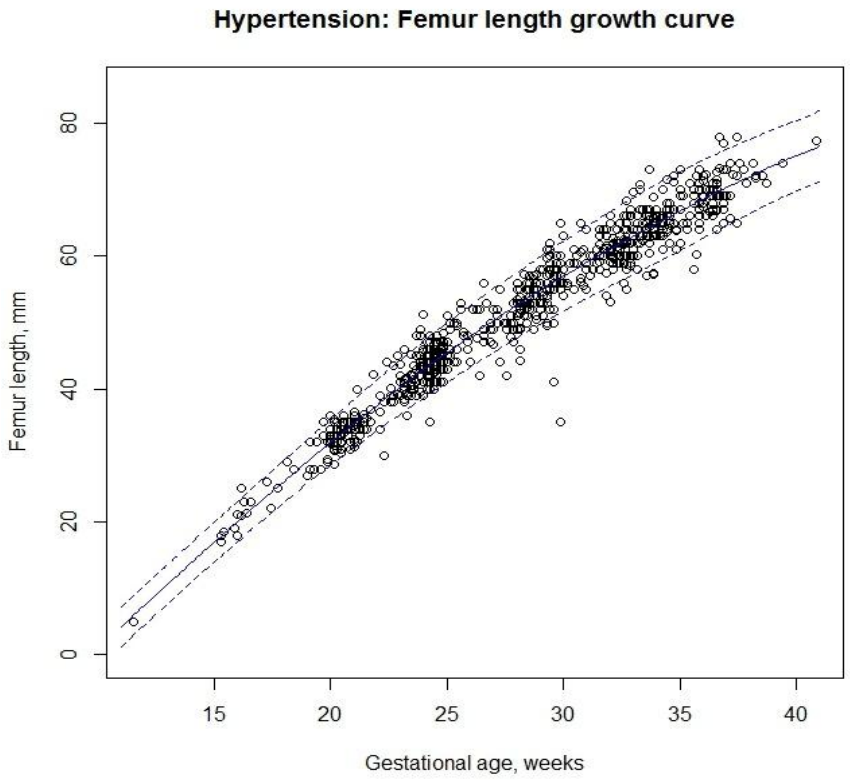



**Figure 4 (a) Femur length scatter diagram (b) transformation by FLDA onto cross sectional charts (Chitty) (c)**



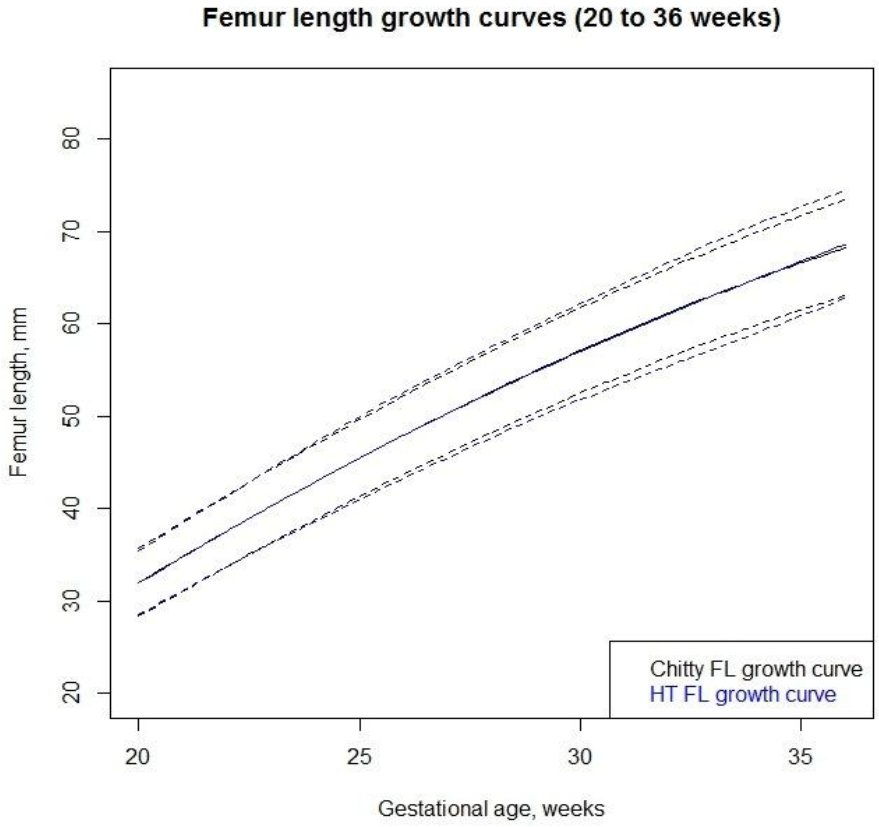
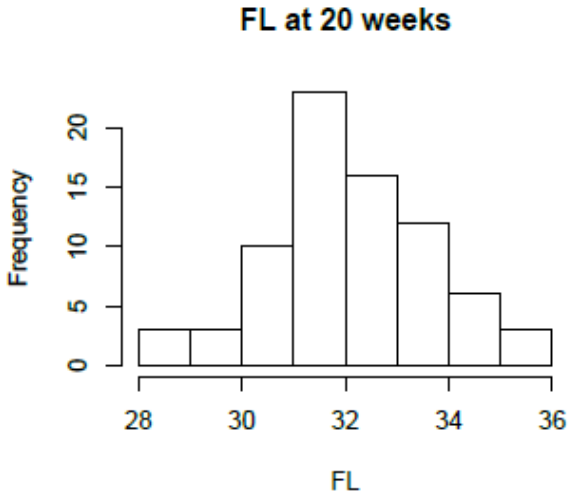
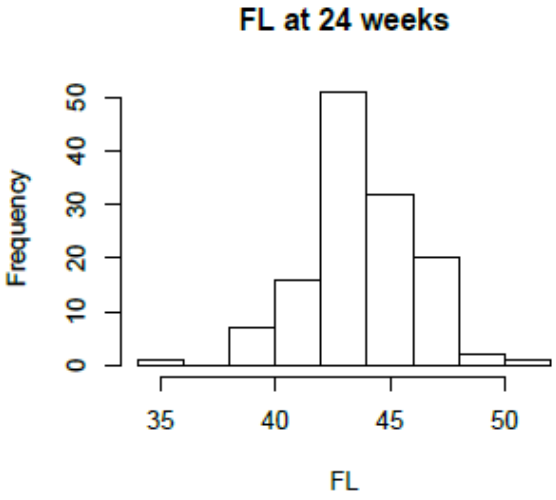
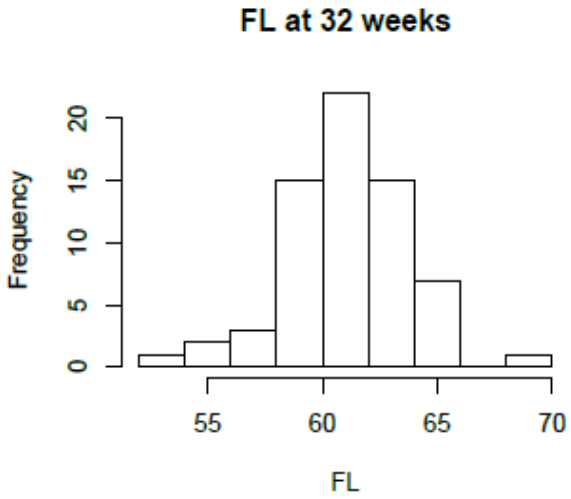



Figure 5 (Suppelementary) – Distribution histograms of the femur length (FL) at 20 and 24 weeks.




21.

**Table 1 Clinical and demographic data and pregnancy outcomes**

*(n=282 unless otherwise stated)*

| | |
|---|---|
| **Maternal age** (years; mean ± SD) | 34 ± 5 |
| **Maternal BMI** (mean ± SD; n=258) | 28 ± 7 |
| **Maternal ethnicity** (n=281) | White European 78 % |
| | African-Caribbean 11% |
| | Asian 11% |
| **Maternal parity** (Median, range; n=278) | 1 (0-6) |
| **Smoking** (n=278) | 4.3% |
| **Regular Alcohol use** (n=278) | 5.3% |
| **Gestational age at delivery** (weeks; mean ± SD) | 37.5 ± 2.78 |
| **Deliveries before 34 weeks** | n=11 3.9% |
| **Deliveries before 37 weeks** | n=37 13.1% |
| **Birthweight (g)** | 3049 ± 785 |
| **SGA < 10th percentile** | 15.6% |
| **LGA >90th percentile** | 20.2% |
| **Delivery type** | Caesarean 48%<br>Vaginal Delivery 52% |
| Fetal **Sex** | Male 51% |
| **Stillbirths** (n=2) | 0.7% |
| **Median Apgar score at 5 minutes** | 9 |
| **NICU admission** (n=46) | 16.3% |
| **Gestational Diabetes** (n=33 ) | 12% |
| **Preeclampsia** (n=36) | 12.8% |
| **HELLP** (n=3) | 1.1% |

**Table 2: Number of ultrasound biometry measurements for abdominal circumference (AC), head circumference (HC) and femur length (FL).**

| Measurement type | Number of cases with number of scans available | | | | | Total number of cases |
|---|---|---|---|---|---|---|
| | 2 scans | 3 scans | 4 scans | 5 scans | 6 scans | |
| AC | 52 | 67 | 58 | 35 | 11 | 223 |
| HC | 55 | 65 | 60 | 33 | 10 | 223 |
| FL | 52 | 67 | 58 | 35 | 11 | 223 |

**Table 3: Growth Velocity for AC, HC and FL (mm/day)**

*p <0.05 compared to the corresponding value for the normal population

#p <0.01 compared to the corresponding value for the normal population

| | Parameter | 26-28 weeks | 30-32 weeks | 34-36 weeks |
|---|---|---|---|---|
| Normal population (derived from Verburg UOG 2008) | AC | 1.526 | 1.357 | 1.140 |
| | HC | 1.466 | 1.177 | 0.826 |
| | FL | 0.332 | 0.269 | 0.198 |
| Chronic hypertension | AC | 1.530 | 1.447* | 1.325# |
| | HC | 1.425 | 1.177 | 0.874 |
| | FL | 0.338 | 0.296# | 0.248# |

HIGHLIGHTS

- Mean birthweight is no different in women with chronic hypertension
- SGA and LGA babies are significantly over-represented in hypertensive pregnancies
- Growth velocity of the abdomen and femur is greater in hypertensive women
- Wider percentile ranges can be found in chronic hypertension

22.